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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,824	11/09/2005	Abraham Hochberg	HOCHBERG1A	4589

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BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
QIAN, CELINE X	
ART UNIT	PAPER NUMBER
1636	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,824	HOCHBERG ET AL.	
	Examiner	Art Unit	
	CELINE X. QIAN	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 13-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0707*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11 and 14-17 are pending in the application.

Election/Restrictions

Applicant's election with traverse of PSA as the tumor marker and prostate cancer as solid tumor for the species election in the reply filed on 10/6/08 is acknowledged. The traversal is on the ground(s) that the generic claims themselves define the same or corresponding special technical features, and the reason given in the previous office action does not relate to PCT Rule 13.1 and 130.2. This is not found persuasive because the legal standard for determining lack of unity between the claimed species is based on PCT Rule 13.1 and 13.2. As explained in the previous office action, the different types of cancer each is a different disease and has different mechanism and symptoms, which is structurally and mechanistically different from each other, thus lack a common special technical feature. Similarly, the markers recited in claim 5 has different structural and function and does not share a same or corresponding technical feature. Applicants fail to provide specific reason why such reason does not relate to PCT 13.1 or 13.2. Therefore, the requirement is still deemed proper and is therefore made FINAL.

Currently, claims 1-11 and 14-17 are under consideration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 6, 7, 10, 13, 14 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Vogelstein et al (US 6,333,152).

Vogelstein et al. discloses a method to aid in determining a prognosis for a patient with colon cancer, the method comprises the steps of: comparing the level of at least one protein or transcript in a first sample to a second sample, wherein the first sample is of a colonic cancer patient and the second sample is from a normal human, wherein the protein is encoded by a transcript and the transcript is identified by a tag selected from the group consisting of those shown in Table 2, wherein the first and the second sample is a sample selected From the group consisting of blood, urine, feces, sputum and serum; determining a poorer prognosis if the level of the at least one protein or transcript is found to be higher in the first sample than in the second sample (see col.5, lines 56-67 and col. 6, lines 1-2). Vogelstein et al. also discloses probes which may be used in radioassays or array chips for high throughput screening to detect, prognose, diagnose or monitor various pancreatic and colon cells and tissues containing those cells (see col.9, lines 59-65), and for PCR primers for detection of genes or gene transcripts in pancreatic and colon cells. Vogelstein discloses that one of the genes that is upregulated in colon cancer is H19 as listed in Table 2 (see col.16, line 5). Therefore, Vogelstein et al. disclose the instantly claimed invention.

Claims 1-4, 6, 7, 9, 10, 13, 14, 16 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Xu et al (US 6,710,170).

Xu et al. disclose a method for detecting a cancer in a patient comprising the steps of: obtaining a biological sample including blood, sera, sputum, urine or tumor biopsies from a patient; contacting said biological sample with an oligonucleotide that hybridizes to a

polynucleotide that encodes a polypeptide that is a marker for the presence of the cancer such as ovarian cancer; comparing the level of the hybridization to the oligonucleotide with a predetermined cut off value, and determine the presence or absence of the cancer (see col.5, lines 5-15, and col. 53, lines 58-65). The specification further discloses that within certain embodiments, the amount of mRNA is detected via PCR such as RT-PCR (see col. 5, lines 15-16, and col. 57, lines 60-61). Xu et al. also disclose that a cancer may also be detected based on the presence of T cells that specifically react with a tumor protein in a biological sample (see col. 57, lines 1-3), wherein the T cells may be isolated from bone marrow (see col.40, lines 8-12). Xu et al. discloses that the markers for ovarian cancer are listed in Tables II-VII, wherein H19 is listed in Table VI, which is generated from a subtraction library of a metastatic ovarian tumor (see col.65, SEQ ID NO:122). Therefore, Xu et al. disclose the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ariel et al (see IDS), in view of Xu et al.

Ariel et al. teach imprinted H19 oncofetal RNA is a candidate tumor marker for hepatocellular carcinoma (see abstract). Ariel et al. teach that H19 expression is present in 13/18 cases hepatocellular carcinoma, and wherein alpha fetoprotein (αFP) is positive in 9/18 samples (see page 23, 2nd col., result section, 1st and 2nd paragraph). Ariel et al. teach that H19 is co-expressed with αFP (see page 24, 2nd paragraph, lines 1-2). Ariel et al. teach that αFP is a glycoprotein synthesized by the fetal liver and yolk sac, and it is widely used as a tumor marker for the diagnosis and follow up of liver cancer. Ariel et al. teach hepatocellular carcinoma is often associated with a remarkable increase of serum αFP (see pages 24, 1st col., last paragraph). Ariel et al. further teach that the staining of the αFP is often weak in tissue samples, whereas the staining of H19 is more diffuse and positive in more hepatocellular carcinoma samples. Ariel et al. also disclose that their group has developed a method for detection of H19 expressing cells in cytological specimens, such as urine, and suggested that H19 may prove to be useful for the diagnosis of heptocellular carcinoma (see page 24, 2nd col., 4th paragraph).

However, Ariel et al. do not teach detecting H19 mRNA and additional marker of αFP in body fluids of a patient suspected having cancer.

The teaching of Xu et al. was discussed above.

It would have been obvious to one of ordinary skill in the art to develop a method of detecting both H19 and αFP mRNA in body fluids to detect the presence of cancer cells from

hepatocellular carcinoma based on what's known in the prior art as evidenced by Ariel et al. and Xu et al. The teaching of Ariel et al. strongly suggested the potential of H19 being used as a marker for hepatocellular carcinoma, and also already developed a method for detecting H19 in urine samples. The teaching of Ariel et al. also demonstrated that the prior art recognizes αFP is a tumor marker for diagnose heptocellular carcinoma. As such, it would have been obvious to an ordinary skilled in the art to measure both H19 and αFP expression for a more precise diagnosis of hepatocellular carcinoma. Xu et al. has demonstrated that measuring mRNA using techniques such as microarray analysis and PCR analysis is feasible for quantification and comparing the expression of tumor marker genes in body fluids and tissues other than the primary tumor site. Based on the availability of such technology, it would have been obvious to an ordinary artisan to detect mRNA of both H19 and αFP in the method of detecting the presence of cancer cells from hepatocellular carcinoma because detecting mRNA is more sensitive than immunostaining. The level of the skill in the art is high. Absent evidence from the contrary, the ordinary artisan would have been able to combine the finding of Ariel at al. and the technology presented in Xu et al. to reach the claimed method. Therefore, the claimed invention would have *been prima facie* obvious to an ordinary artisan at the time the invention was made.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al., in view of Fronhoffs (Molecular and Cellular Probes, April, 2002. Vol.16, No.2, pages 99-110).

The teaching of Xu et al. was discussed above.

However, Xu et al. do not teach performing an RNA detection assay by adding varying and known amounts of H19 mRNA to a sample to produce a calibration curve showing the level of reading of the RNA detection assay as a function of the known H19 RNA, correlating the

amounts of H19 in the calibration curve to the H19 RNA obtained from a plurality of diagnosed patients of a specific tumor and healthy controls, defining the difference between those as standard threshold H19 level.

Fronhoffs et al. teach a method for the rapid construction of cRNA standard curves in quantitative real-time reverse transcription polymerase chain reaction. Fronhoffs et al. teach a method for generating cRNA standard curves for detecting amount of target RNA in quantitative RT-PCR. Fronhoffs et al. teach a serial dilution of known amount of copy numbers of cRNA are added to sample to generating a standard curve, whereas the target RNA is quantified based on the standard curve (see pages 102, 1st col., 2nd-3rd paragraph, page 104, bridging paragraph of 1st and 2nd col., 2nd col., 2nd-3rd paragraph). Fronhoffs et al. teach that this approach is applicable to any gene of interest and might become a new standard for mRNA quantification.

It would have been obvious to an ordinary skill in the art to apply a RNA detection assay comprising: adding varying and known amounts of H19 mRNA to a sample to produce a calibration curve showing the level of reading of the RNA detection assay as a function of the known H19 RNA, correlating the amounts of H19 in the calibration curve to the H19 RNA obtained from a plurality of diagnosed patients of a specific tumor and healthy controls, defining the difference between those as standard threshold H19 level based on combined teaching of Xu et al. and Fronhoffs et al. At the time of filing, there are a number of method known in the art for quantification of RNA using real time PCR, and generating a standard curve by adding known amount of RNA to the sample is one of these methods as shown by Fronhoffs et al. Since the method presented by Fronhoffs has worked well for rapid and simple quantification of RNA in tissue samples, and it suggests the method may be used for detecting any gene of interest, an

ordinary artisan who is interested in measuring H19 RNA in cancer and healthy individual would adopt this method to quantify RNA present in a patient sample and establish a threshold between normal and cancer patients based on such measurement. Therefore, the claimed invention would have been *prima facie* obvious to an ordinary artisan at the time the invention was made.

Claims 8 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al., in view of Kondo et al (Oncogene.1995. Vol.10, pages 1193-1198) and Ichinose et al. (Ann. Thorac. Surg. 1997. Vol. 64, pages 1626-1629).

The teaching of Xu et al. was discussed above.

However, Xu et al. do not detecting H19 RNA in rinse fluid obtained by rinsing a body cavity such as lung.

Kondo et al. teach loss of imprinting (LOI) of H19 is a frequent event in lung cancer development, and correlated with hypomethylation of the promoter region. Kondo et al. also demonstrate overexpression of H19 is often associated with LOI of H19 in lung cancers retaining both parental alleles (see pages 1194, 2nd col., 1st paragraph, and Figure 4).

Ichinose et al. teach visceral pleural invasion by the tumor is an important prognostic factor in patients undergoing resection for lung cancer. Ichinose et al. teach desquamated cells were collected from a rinse fluid by applying a jet stream of saline solution to the surface of visceral pleura and subject to cytologic analysis. Ichinose et al. teach that when cancer cells are found in the collected fluid, the tumor were judged to have invaded the visceral pleura, wherein the sensitivity reached 87% and 94% (see abstract, and Table 1 and 2).

It would have been obvious to an ordinary skill in the art to performing the method of detecting lung cancer or the presence of lung cancer cells by assessing the expression of H19 in

cancer cells collected from rinsing fluid, such as those rinsing fluid obtained from a body cavity as claimed based on the combined teaching of Xu et al., Kondo et al. and Ichinose et al. Xu et al. have taught a method for detecting a cancer in a patient comprising the steps of: obtaining a biological sample including blood, sera, sputum, urine or tumor biopsies from a patient; contacting said biological sample with an oligonucleotide that hybridizes to a polynucleotide that encodes a polypeptide that is a marker for the presence of the cancer such as ovarian cancer; comparing the level of the hybridization to the oligonucleotide with a predetermined cut off value, and determine the presence or absence of the cancer (see col.5, lines 5-15, and col. 53, lines 58-65). Xu et al. also teach this method may be adapted to other types of cancer wherein H19 is elevated. Such observation is indeed demonstrated by Kondo et al., which report the LOI and overexpression of H19 in lung cancers. Ichinose et al. demonstrated that rinsing fluid from visceral pleura having tumor invasion contains cancer cells wherein the detection of said cells in rinsing fluid is sensitive. As such, the ordinary artisan would have been motivated to use rinsing fluid as an alternative to body fluids to detecting H19 expression in cancer cells. The level of skill in the art is high as evidenced by the sensitive detection of gene expression by quantitative RT-PCR as demonstrated by Xu et al. The ordinary skill in the art would have reasonable expectation of success to detect H19 expression in rinsing fluid collected from body cavity wherein cancer cells are present. Therefore, the claimed invention would have been *prima facie* obvious to the ordinary artisan at the time the invention was made.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE X. QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian /
Primary Examiner, Art Unit 1636